Implementation, Data Analysis, and Support for Toxics Release Inventory (TRI)
Contract No. GS-00F-252CA, Task Order #EP-G18H-01464
Technical Directive: Assigned by TD Level-COR, **Under Task(s):** 1, 2, 3, 7, 8, 9, 11, and 12

Title: General Support for TRI Program Analyses and TSCA-Related Projects

Period of Performance: December 29, 2017 – December 28, 2018

BACKGROUND

Under the Emergency Planning and Community Right to Know Act (EPCRA), the Toxics Release Inventory (TRI) program authorized under Section 313 requires subject facilities to submit data annually on toxic chemical use and management. This information is organized into a database by EPA and is currently made available to the public through the TRI website in spreadsheets, in a variety of access and analysis tools, and in the TRI National Analysis. TRI access and analysis tools make TRI data more accessible for the public and for EPA employees.

EPA's TRI Program has a long history of providing both internal and external users of TRI data and information with ad hoc analytical support and technical expertise. The TRI Program routinely conducts analyses in support of the Program's own projects and undertakings, or those from offices within EPA or other parts of the federal government. The types of analyses include, for example, chemical specific, industry specific, facility specific, location specific, emission inventory related analyses, and risk related analyses, to name a few. These analyses have also involved the use of other pollutant release and transfer registries (PRTRs) and they are often directly or indirectly related to EPA's annual TRI National Analysis and/or other priority projects. Not only do these expert analytical and consultative analyses benefit others, these services can also lead to the identification of new applications and uses of TRI data and collaborations.

An EPA priority set by the immediate office of the Office of Pollution Prevention and Toxics (OPPT) is to carry out the mandates of the Toxic Substances Control Act (TSCA), which now includes new requirements and statutory deadlines for actions related to the regulation of existing and new chemical substances and mixtures in the United States. This recently enacted amendment to TSCA, the Frank R. Lautenberg Chemical Safety for the 21st Century Act (LCSA), calls for the selection of existing TSCA inventory chemicals that because of their toxicity or exposure potential warrant prioritization for further in-depth review, evaluation, and possible risk management actions. A previous screening effort by EPA has developed a list of prospective chemical candidates for further assessment, in so named the TSCA Work Plan chemicals. These Work Plan chemicals all scored high based on a combined screening method which incorporated hazard, exposure, and persistence and bioaccumulation characteristics. This Work Plan of chemicals helps to focus and direct the activities of implementing new TSCA for existing chemicals, which are to be evaluated against a new risk-based safety standard to determine whether a chemical poses an unreasonable risk of injury to health or the environment, without consideration of costs or other non-risk factors, including an unreasonable risk to a potentially exposed or susceptible subpopulation, under its conditions of use.

Many of these existing chemicals share great congruency with the TRI Program and the TRI list of toxic chemicals in that virtually all of the chemicals included on the TRI list can be found on the TSCA inventory. In addition, of the previously identified TSCA Work Plan chemicals (90 in total), 60 of them are included on the TRI list of toxic chemicals. This has provided a unique opportunity to promote the utility of TRI data as an information resource for existing TSCA chemicals and to collaborate closely with other program offices within and outside of OPPT to conduct expert analyses and technical support for a variety of purposes and needs relevant to risk-based decision making and chemical characterization under amended TSCA.

Not only are the new requirements under the Lautenberg Act amendments to TSCA mandated for existing chemicals, but now EPA must also make affirmative findings on the safety of new chemicals or significant new uses of an existing chemical before it is allowed into the marketplace under Section 5 of TSCA. Conducting premanufacture notice (PMN) reviews and risk evaluations for newly introduced chemicals or uses mirrors the same underlying risk context considerations for safety standards as existing chemicals listed on the TSCA inventory, however, there exists an important dilemma when assessing newly synthesized chemicals. This predicament is shrouded in the many uncertainties that are introduced when evaluating new chemical substances that have insufficient, scarce, or sometimes completely absent hazard, safety, and/or test data information. This concern has heightened the need for and importance of scientifically valid, efficient, and rapid alternative hazard assessment and predictive methodologies. EPA uses a variety of approaches to assess chemical hazard, which include nearest analog analysis, chemical class analogy, (quantitative) structure-activity relationships ((Q)SARs), and mechanisms of toxic action. All of these alternative toxicity testing methods (ATMs) help to screen, characterize, and prioritize chemical substances that might inflict harmful effects upon heath and/or the environment.

In 2005, the EPA, with support from the National Institute of Environmental Health Sciences (NIEHS) and the National Toxicology Program (NTP), asked the National Research Council (NRC), the nation's leading organization known for providing independent expert advice on matters of science, technology, and medicine, to develop a long-range vision for toxicity testing and a strategic plan to accomplish it. The NRC released its report in 2007, *Toxicity Testing in the 21st Century: A Vision and a Strategy*. The report called for strong emphasis on moving the field of toxicology from a predominantly observational science at the level of disease-specific, apical models to a predominantly predictive science focused upon a broad inclusion of target-specific, mechanism-based, biological observations. The key proposal of TOX 21 is simple: regulatory toxicology for environmental chemicals needs to be based on mechanisms and modes of action. Toxicity testing should not only focus on the toxic effects that chemicals can have on human health and the environment, but also how these chemicals impart these toxic effects.

In order to put the goals and principles of Tox21 into practice, part of the discussion now has to focus on deciding what types and combinations of ATMs should be used to better predict, classify, and evaluate the effects that chemicals can have with more certainty and on how to organize and compile these knowledge bases. As stipulated under LCSA, risk assessors and chemical regulators alike are to rely less on animal toxicity studies and focus more on harnessing *in vitro* methods, *in silico* approaches, and integrated testing strategies (ITS) to implement new TSCA. The ultimate vision over time is to incorporate these so called new approach methodologies (NAMs) into the regulatory and toxicity testing paradigm, which will usher in new opportunities to anticipate undesirable toxicological effects of chemicals and enhance the prioritization, evaluation, management, and safety of new and existing chemicals in the U.S.

PURPOSE

The purpose of this task order is to obtain Contractor support for analyses or research in provision of the TRI Program's own projects and undertakings or those from offices within EPA or other parts of the federal government.

It is not known at this time specifically what analyses or information may or will be needed, or if it will be needed. Some analyses and information development will be assigned to the Contractor on an as needed basis by the TD-COR, and will be within the scope of the Technical Directive. The TD-COR will provide the Contractor with specific guidance and direction for the analyses and the specific information or data that is to be developed. This work will build upon the research and publications of current and past Agency employees. If deemed appropriate by the EPA TD-COR, subject matter experts within or outside of EPA, will be identified and consulted in the development of the deliverables under this work assignment.

SCOPE OF WORK

The contractor shall provide support to the Environmental Protection Agency's TRI Program. In particular, the contractor shall provide support for the tasks listed below.

Task 1 – Prepare Work Plan
Task 1a. The Contractor shall prepare a work plan within **15** calendar days of receipt of this Technical Directive. The work plan shall outline and describe the technical approach, resources (cost estimates and staffing), and a schedule for submitting deliverables to EPA.
Task 1b. If necessary, the Contractor shall revise the work plan within 5 calendar days of receipt.

Task 2 – Explore and Investigate the Incorporation of Novel Data Streams into Chemical Prioritization and Chemical Assessments for TRI and TSCA-Related Support.
In reference to the Contract Statement of Work, this task falls under Section 1 ("Conduct TRI and Related Analyses") and Section 2 ("Enhance Data Quality").

There is growing interest in exploring the feasibility of using novel data streams, specifically data from the federal government's Tox21 program, to inform chemical prioritization and assessments for TRI and for TSCA-related support. The federal government developed the Tox21 program to more efficiently screen, prioritize, and evaluate chemicals based on their biologic activity in various assays. Tox21 pools resources from several federal agencies including EPA, the National Institutes of Environmental Health Sciences/National Toxicology Program, and the Food and Drug Administration, and uses high throughput screening (HTS) technology to assess thousands of chemicals for potential toxicity. EPA's contribution to Tox21 is referred to as Toxicity Forecaster (ToxCast), which is run by EPA's National Center for Computational Toxicology (NCCT) within the Office of Research and Development (ORD). Under the Tox21 program, automated chemical screening technologies are used to expose living cells or isolated proteins to chemicals. The cells or proteins are then screened for changes in biological activity that may suggest potential toxic effects and eventually potential adverse health effects. Tox21 has evaluated over 10,000 chemicals to date while EPA has screened approximately 2,000 chemicals through ToxCast.

Similar to the effort described in a previous memorandum from August, 2015 titled *Proposed Approach for Assessing the Feasibility of Using Tox21 Data to Inform Safer Chemical Design*, submitted by the Contractor to EPA, the Contractor shall evaluate the feasibility of using data developed under the Tox21 program to support TRI-related efforts (Task 2a) and TSCA-related efforts (Task 2b). Because there are now HTS data not previously available for thousands of chemicals, the potential exists to move the field of chemical assessment forward, especially in regard to identifying, classifying, and grouping inherent chemical hazards via alternative toxicity testing methods. However, how reliable this information can be for a human health assessor, toxicologist, or other risk assessor responsible for risk evaluations under TRI or new TSCA has not been explored. If through this work it is deemed that using the Tox21 program data can inform TRI and/or TSCA-related support, a case study demonstrating the proposed approach should be conducted.

Task 2a. The TRI chemical list offers an opportunity to apply *in vitro* and HTS data generated by the U.S. federal government's Tox21 program and the U.S. EPA's ToxCast program. Of the 675 chemicals included on the TRI list of toxic chemicals, 506 have been screened by the Tox21 program. Of these 506 TRI chemicals, 298 have also been evaluated through EPA's ToxCast program. Much insight could be gained from an analysis and integration of available *in vitro* and *in vivo* toxicity data, pharmacokinetic data and HTS data, with the intent of elucidating structure-toxicity relationships in support of TRI-related efforts (ex. identifying safer alternatives to TRI-listed chemicals).

Task 2b. EPA also anticipates additional work to complete an ongoing strategic plan and projects focused on exploring the feasibility of incorporating HTS data and/or other alternative test methods or strategies that do not require new vertebrate animal testing and are scientifically reliable, relevant, and capable of providing information of equivalent or better scientific reliability and quality to that which would be obtained from typical vertebrate animal testing. Support to this strategic plan of promoting the development and implementation of ATMs, NAMs, and novel data streams into chemical risk assessments under new TSCA can enrich the prioritization and evaluation of existing TSCA Work Plan chemicals as well as new chemicals submitted under Section 5 of TSCA.

Task 3 – Compile Structural/Mechanistic Alerts of Toxic Concern and Research Predictive Tools, Models, and Databases.
In reference to the Contract Statement of Work, this task falls under Section 1 ("Conduct TRI and Related Analyses") and Section 2 ("Enhance Data Quality").

There is a mutualistic relationship between novel data streams (i.e. ATMs and NAMs) and a comprehension of the structural and mechanistic underpinnings of the biological action of toxic chemicals. When combined properly, not only are they able to generate much more toxicologically relevant data, but they can also expand the number of chemicals that can be scrutinized and bring clearer and more transparent communication of potential adverse effects to light. Regulatory toxicology for environmental chemicals needs to be based on mechanisms and modes of action to provide better hazard identification of intrinsic toxicities. Intrinsic toxicities are the tendencies of chemical substances to cause alterations in normal cellular biochemistry and physiology, and are usually attributable to a particular structural portion of the substance which is commonly referred to as a structural alert (SA). Substances that contain these SAs are apt to produce a certain biological effect depending on the nature of their function and intended use. The chemicals that share similar moieties can be grouped or categorized because they are likely to elicit similar toxicological effects or follow a regular pattern of toxicity. The Organization for Economic Co-operation and Development (OECD) has recommended that chemical substances be grouped on the basis of either structural analogs, mechanistic analogs, or mode of action analogs.

Task 3a. There has been an increasing understanding of modes of toxic action and the underlying (bio)chemical mechanisms for chemical substances and mixtures using available SAs, mechanistic data, and (Q)SAR models throughout recent years. The Contractor shall evaluate and compile a comprehensive list of available structural and mechanistic alerts of potential toxicological concern that can be used to support relevant TRI and TSCA-related efforts.

This increased understanding of mechanisms of toxic action is the result of advancements in computational modeling, HTS, systems biology, and bioinformatics of compounds in receptor and toxicity-related assays. This transformative evolution of using computer technology and mathematical tools/software for data mining and analysis has also catalyzed dramatic improvements in predictive toxicology, hazard identification, and analog selection. EPA has developed over the years predictive models and tools (ex. OncoLogic, ECOSAR, EPI Suite…etc) and databases to help evaluate and catalog what happens to chemicals when they are used and released to the environment and how workers, citizens, and the environment might be exposed to and affected by them. The information contained in these various predictive models and databases can provide a wealth of knowledge that can complement chemometric-based mechanistic (Q)SAR studies for ideal integrative chemical assessment. This can lead to a greater ability of properly classifying and grouping chemical substances and selecting the most appropriate molecular descriptors and chemical analogs.

Task 3b. EPA recognizes the need to conduct a comprehensive review of predictive toxicology models, tools, and databases that support rapid hazard identification and analog selection of chemical substances. The Contractor shall research and report available predictive methodologies, software, and

databases (both within and outside of OPPT) that are considered relevant to support TRI and TSCA-related efforts.

Task 4 – Provide Analysis and Support for Updating EPA's Chemical Categories of Concern
In reference to the Contract Statement of Work, this task falls under Section 1 ("Conduct TRI and Related Analyses") and Section 2 ("Enhance Data Quality").

There are many ways to categorize or group chemical substances. The OECD has developed guidance documents for category and grouping approaches to strategize and facilitate hazard assessments and toxicity testing. A substance category is defined as a group of substances whose physicochemical, toxicological, and/or environmental fate properties are likely to be similar or follow a regular pattern as a result of structural or mechanistic similarity. The rationale for forming the category may be based on a range of characteristics such as common functional group(s), common constituent(s), chemical classes with a defined chain-length, likelihood of having common precursor and/or breakdown products, or a particular reaction chemistry domain. The assessment of substances by using a category approach differs from the approach of assessing them on an individual basis because the effects of the individual substances within a category are assessed on the basis of the evaluation of the category as a whole, rather than on measured data for any one particular substance alone, especially when data on that individual substance are scarce or absent. As a form of weight of evidence (WOE) approach, categorical approaches typically integrate both estimated and experimental data with the application of expert judgment. The biggest challenge in these approaches rests in defining the categories themselves (their underlying rationale/mechanistic basis) and in particular their boundaries.

EPA groups existing and new chemicals with shared chemical and toxicological properties into "chemical categories of concern", which enables EPA reviewers and others to benefit from the accumulated data and past decisional precedents allowing assessments to be facilitated. Each category of concern has a definition of chemical structure and limitation of members, hazard concerns, boundaries of size and route of exposure, occupational exposure controls, and toxicity testing. These chemical categories of concern have been continuously updated over the years with the latest update in August, 2010.

The enactment of LCSA has brought a sharp focus on, and the establishment of priorities for, those chemicals and chemical classes of greatest concern to human health and the environment. Being that the chemical categories of concern have not been updated in quite some time, there exists a potential opportunity to refine, expand, or create new chemical categories of concern that can be of great value to risk assessors. Not only are these categories of concern in need of an update, but here lies a great instance to assimilate prospective NAMs, ATMs, and novel data stream information into relevant TSCA needs for existing and new chemicals. Utilizing these new data sources in combination with qualitative recognitions of SARs and SAs, research needs and toxicity data gaps can be identified and eventually filled in by means of *reading-across* or inferring endpoint information of a target chemical based on the properties of a similar chemical analog. As more data gaps become filled in using predictive tools and models, trends or signatures of the data may become more apparent, which could lead to a more robust mechanistic knowledge of the biological action of chemical substances. This enhanced knowledge can ultimately be used to elucidate additional chemical descriptors, mechanistic alerts, and/or bioactivity descriptors and be used to group and classify chemicals in the near future.

It is not known at this time specifically what analyses or information may or will be needed for updating the chemical categories of concern. Some analyses and information development will be assigned to the Contractor on an as needed basis by the TD-COR, and will be within the scope of the Technical Directive. The TD-COR will provide the Contractor with specific guidance and direction for the analyses and the specific information or data that is to be developed.

Task #5: Conduct Ad Hoc Analytical Support for TRI Program Projects and Activities, and for TRI Program Customers

In reference to the Contract Statement of Work, this task falls under Sections 1 ("Conduct TRI and Related Analyses") and 2 ("Enhance Data Quality").

EPA's TRI Program has a long history of providing both internal and external users of TRI data and information with ad hoc analytical support and technical expertise for activities involving EPA's TRI database and other pollutant release and transfer registers or emission inventories. Many of these analyses are related to exposure to the chemicals included on the TRI list of toxic chemicals, and the risks posed by such exposures. The TRI Program also routinely conducts analyses in support of the program's own projects and undertakings or those of from offices within EPA or other parts of the federal government. These analyses may involve the use of other pollutant release and transfer registries, and to support the international activities for which the TRI Program is involved.

It is not known at this time specifically what analyses or information may or will be needed, or if it will be needed. Analyses and information development will be assigned to the Contractor on an as needed basis by the TD-COR, and will be within the scope of the Technical Directive. The TD-COR will provide the Contractor with specific guidance and direction for the analyses and the specific information or data that is to be developed.

DELIVERABLE SCHEDULE

Unless otherwise directed by the TD-COR, all deliverables will be in Microsoft Word and/or Excel spreadsheet format.

TASKS	ASSIGNMENTS	DUE DATE
1a. **1b.**	Prepare work plan Revise work plan if necessary	15 calendars day of receipt 5 calendar days of receipt
2a. **2b.**	Explore feasibility of integrating novel data streams in support of TRI-related efforts Investigate the potential incorporation of novel data streams into chemical risk assessments under new TSCA	Per directions of TD-COR
3a. **3b.**	Compile available structural and mechanistic alerts of potential toxicological concern for TRI and TSCA-related support. Conduct a comprehensive review of predictive toxicology models, tools, and databases that support rapid hazard identification and analog selection of chemical substances.	Per directions of TD-COR
4.	Provide analysis and support for updating EPA's Chemical Categories of Concern	Per directions of TD-COR
5.	Conduct ad hoc analytic support for TRI Program projects and activities, and for TRI Program customers	Per directions of TD-COR

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